

CLAIMS

1. An altered IGFBP molecule able to effect binding of IGF-I or IGF-II with high affinity characterised in having an inhibited release of IGF on contact with extracellular
5 matrix or exposure to a protease.
2. An altered IGFBP molecule as in claim 1 wherein the IGFBP is ISGFBP-2.
3. An altered IGFBP molecule of claim 2 wherein the IGFBP-2 molecule has an
10 alteration in one or more amino acids of a first ECM binding sequence which spans amino acids 179-184 and comprises the sequence PKKLRP [SEQ ID No 1].
4. An altered IGFBP molecule as in either claim 2 or 3 wherein the altered IGFBP-2 molecule has an alteration in one or more amino acids of a second ECM binding
15 sequence which spans amino acids 227-244 and comprises the sequence KHGLYNLKQCKMSLNGQR [SEQ ID No 2].
5. An altered IGFBP molecule as in claim 3 wherein the alteration in the first ECM binding sequence is selected from the group consisting of SEQ ID No 9, SEQ ID No 10,
20 SEQ ID No 11, SEQ ID No 12 and SEQ ID No 13.
6. An altered IGFBP molecule as in claim 4 wherein the alteration in the second ECM binding sequence is selected from the group consisting of SEQ ID No 14, SEQ ID No 15, SEQ ID No 16, SEQ ID No 17 and SEQ ID No 18.
25
7. An altered IGFBP molecule as in claim 2 wherein the amino acid sequence is altered as one or both of K180A and K181A
8. An altered IGFBP molecule as in either claim 3 or 4 wherein the IGFBP-2
30 molecule has additionally an alteration of its amino acid sequence that enhances resistance to proteolysis by one or more proteases.

9. An altered IGFBP molecule as in claim 8 wherein the IGFBP-2 molecule has an amino acid sequence altered in the linker domain to provide resistance to said one or more proteases.
- 5 10. An altered IGFBP molecule as claim 8 having one or more amino acids deleted within the linker domain
11. An altered IGFBP molecule as claim 8 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180
10 through to 191.
12. An altered IGFBP molecule as in claim 8 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.
- 15 13. An altered IGFBP molecule as in claim 2 wherein the IGFBP-2 molecule additionally has an amino acid sequence altered to enhances resistance to proteolysis by one or more proteases.
14. An altered IGFBP molecule as in claim 2 wherein the IGFBP-2 molecule has an
20 amino acid sequence alteration in the linker domain to provide resistance to said one or more proteases.
15. An altered IGFBP molecule as claim 2 having one or more amino acids deleted within the linker domain
25
16. An altered IGFBP molecule as claim 2 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.
- 30 17. An altered IGFBP molecule as in claim 2 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.

18. An altered IGFBP molecule as in claim 14 wherein the amino acid sequence is altered at one or both positions as follows K180A and K181A.

19. A nucleic acid encoding an altered IGFBP molecule said altered IGFBP molecule
5 able to effect binding of IGF-I or IGF-II with high affinity characterised in having an inhibited release of IGF on contact with extracellular matrix or exposure to a protease.

20. A nucleic acid encoding an altered IGFBP molecule as in claim 19 wherein the IGFBP is ISGFBP-2.

10

21. A nucleic acid encoding an altered IGFBP molecule as claim 20 wherein the IGFBP-2 molecule has an alteration in one or more amino acids of a first ECM binding sequence which spans amino acids 179-184 and comprises the sequence PKKLRP [SEQ ID No 1]

15

22. A nucleic acid encoding an altered IGFBP molecule as in either claim 20 or 21 wherein the altered IGFBP-2 molecule has an alteration in one or more amino acids of a second ECM binding sequence which spans amino acids 227-244 and comprises the sequence KHGLYNLKQCKMSLNGQR [SEQ ID No 2].

20

23. A nucleic acid encoding an altered IGFBP molecule as in claim 21 wherein the alteration in the first ECM binding sequence is selected from the group consisting of SEQ ID No 9, SEQ ID No 10, SEQ ID No 11, SEQ ID No 12 and SEQ ID No 13.

25

24. A nucleic acid encoding an altered IGFBP molecule as in claim 22 wherein the alteration in the second ECM binding sequence is selected from the group consisting of SEQ ID No 14, SEQ ID No 15, SEQ ID No 16, SEQ ID No 17 and SEQ ID No 18.

25. A nucleic acid encoding an altered IGFBP molecule as in claim 20 wherein the
30 amino acid sequence is altered in one or both of K180A and K181A

26. A nucleic acid encoding an altered IGFBP molecule as in either claim 21 or 22 wherein the IGFBP-2 molecule has additionally an alteration of its amino acid sequence that enhances resistance to proteolysis by one or more proteases.
- 5 27. A nucleic acid encoding an altered IGFBP molecule as in claim 26 wherein the IGFBP-2 molecule has an amino acid sequence alteration in the linker domain to provide resistance to said one or more proteases.
28. A nucleic acid encoding an altered IGFBP molecule as claim 26 having one or
10 more amino acids deleted within the linker domain.
29. A nucleic acid encoding an altered IGFBP molecule as claim 26 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.
- 15 30. A nucleic acid encoding an altered IGFBP molecule as in claim 26 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.
31. A nucleic acid encoding an altered IGFBP molecule as in claim 26 wherein the
20 IGFBP-2 molecule additionally has an amino acid sequence altered to enhance resistance to proteolysis by one or more proteases.
32. A nucleic acid encoding an altered IGFBP molecule as in claim 20 wherein the IGFBP-2 molecule has an amino acid sequence altered in the linker domain to provide
25 resistance to said one or more proteases.
33. A nucleic acid encoding an altered IGFBP molecule as claim 20 having one or more amino acids deleted within the linker domain
- 30 34. A nucleic acid encoding an altered IGFBP molecule as claim 20 wherein substantially all of the linker domain is deleted, but said altered molecule still retains amino acids from about 180 through to 191.

35. A nucleic acid encoding an altered IGFBP molecule as in claim 20 wherein the IGFBP-2 molecule has a deletion of amino acids 114 through to 170.

5 36. A nucleic acid encoding an altered IGFBP molecule as in claim 31 wherein the amino acid sequence is altered at one or both positions as follows K180A and K181A

37 A nucleic acid encoding an altered IGFBP molecule as in any one of claims 19 to 36 wherein the nucleic acid is a vector, the vector having nucleic acid operably linked
10 with a control sequence including a promoter for transcription leading to expression of the altered IGFBP.

38. A host cell carrying a nucleic acid as in any one of claims 19 to 37

15 39. A method of reducing IGF mediated proliferation of a population of cancerous cells, the method including the step of contacting the population of cells with an altered IGFBP as in any one of claims 1 to 18.

40. The method of reducing IGF mediated proliferation of a population of cancerous
20 cells as in claim 39 wherein the cancerous cells are selected from the group consisting of prostate, colon and breast cancer cells.

41. The method of reducing IGF mediated proliferation of a population of cancerous cells as in claim 39 wherein the cancerous cells are colon cancer cells.